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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,877	08/08/2002	Daniel Henry Densham	GJE-89	1425

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	10/089,877	DENSHAM, DANIEL HENRY	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26,28,30,32-35,41,43,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26,28,30 and 32-35* is/are rejected.

7)☐ Claim(s) *41,43,45 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/10/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed on July 19, 2004 is acknowledged and has been entered. Claims 22, 28, 30, 34, 41 and 43 have been amended. Claims 1-21, 27, 29, 31, 36-40, 42 and 44 have been canceled. Claim 46 has been added. Claims 22-26, 28, 30, 32-35, 41, 43 and 45-46 are pending. All of the amendments and arguments have been thoroughly reviewed and considered but are deemed moot in view of the new grounds of rejections based on Applicant's amendments of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Objections and Rejections

3. The objection to the specification for the use of an improper sequence identifier is withdrawn in view of Applicant's amendment of the specification at pages 12 and 13. The claim rejection under 35 USC 112 second paragraph directed to claim 22-35 for the lack of a final process step is withdrawn in view of Applicant's amendment of claim 22. The claim rejection under 35 USC 112 second paragraph directed to claims 22, 28, 40 and 41 for the recitation of "capable of" is withdrawn in view of Applicant's amendment of the claims. The prior art rejection under 35 USC 102(b) directed to claims 22, 23 and 25 as being anticipated by Holzrichter et al is withdrawn in view of Applicant's amendment of the claims. The claim rejection under 35 USC 102(e) directed to claims 22-27, 29, 31, 32, 34, 36-45 as being anticipated by Chan et al ('896) is withdrawn in view of Applicant's amendment to the claims.

The prior art rejection under 35 USC 102(e) directed to claim 33 as being anticipated by Chan et al ('420) is withdrawn in view of Applicant amendment. The prior art rejection under 35 U.S.C. 103(a) directed to claims 28, 30, 35 as being unpatentable over Chan et al in view of Ha et al is withdrawn in view of Applicant's amendment to the claims

New Ground(s) of Rejections

THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Objections

2. Claims 41, 43, 45 and 46 are objected to because of the following informalities: Claims 41, 43, 45 and 46 are objected to for the abbreviation "FRET" because abbreviations often have more than one meaning in the art. It is suggested inserting the full name of the abbreviation into the claim as supported by the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 22-26, 28, 30, 32-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 22-26, 28, 30, 32-35 are indefinite at the recitation of "first fluorescent molecule" because the claims appear to require multiple bound fluorescent molecules attached to the enzyme; however, it unclear if the "bound label", as recited in the dependent claims 28 and 30, is

a fluorescent molecule that relates to or is sequential to the first bound fluorescent molecule or if the "bound label" is in reference to some other molecule. Clarification is required.

(b) Claims 28, 30 and 34 lacks proper antecedent basis at "the first fluorescent molecule" because claim 22 from which they depend does not recite "a first fluorescent molecule" but recites "a first bound fluorescent molecule". It is suggest amending the claims such that the claim languages agree.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 22-23, 25, 28, 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Korlach et al (US 2003/0044781 A1, effective filing date May 19, 1999). Regarding claim 26, Korlach et al teach a method for determining the sequence of a polynucleotide comprising the steps: (i) reacting a target polynucleotide with an enzyme that interacts with and processes along the polynucleotide, under conditions sufficient to induce enzyme activity; and (ii) detecting conformation changes in the enzyme as the enzyme processes along the polynucleotide, and thereby determining the sequence of the polynucleotide, wherein the enzyme comprises a first bound fluorescent molecule, the characteristic of which alters as the enzyme undergoes a conformation change, and wherein the target does not comprise a label (paragraphs 0074, 0105 and 0067, especially col. 2, lines 19-23).

Regarding claim 23, Korlach et al teach the method according to claim 22, wherein the enzyme is a polymerase enzyme (paragraphs 0042, 0074, 0105).

Regarding claim 25, Korlach et al teach the method according to claim 22, wherein the enzyme is immobilized on a solid support (paragraph 0074).

Regarding claim 28, Korlach et al teach a method according to claim 22, wherein the enzyme comprises a label that interacts with a first fluorescent molecule[1], wherein the degree of interaction is dependent on a conformational change in the enzyme ((paragraphs 0074, 0105 and 0067).

Regarding claim 30, Korlach et al teach a method according to claim 28, wherein the first fluorescent molecule is an energy acceptor and the bound label on the enzyme is an energy donor and wherein step (ii) is carried out by measuring energy transfer between the first fluorescent molecule and the bound label (paragraph 0105).

Therefore, Korlach et al meets the limitations of claims 22, 23, 25, 28 and 30 of the instant invention.

Claim Rejections - 35 USC § 103

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 24, 26, 32, 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korlach et al as previously applied above to claims 22-23 and 25, in view of Chan et al (US 6, 210,896 B2, effective filing date August 13, 1998). Regarding claim 24, Korlach et al teach a method for determining the sequence of a polynucleotide comprising the embodiments discussed in claim 22, wherein the enzyme is a polymerase enzyme (paragraphs 0042, 0074, 0105). Korlach et al further teach wherein the polymerase enzyme may further comprise an accessory protein, such as e.g., a helicase or primase, to enhance processivity of the target/enzyme complex (paragraph 0074, page 10, col. 1, lines 15-21).

Korlach et al differ from the instant invention in that the reference does not teach wherein the enzyme of the sequencing method is a helicase or primase.

Chan et al teach a method similar to that of Korlach et al for determining the sequence of a polynucleotide, the method comprising: (i) reacting a target polynucleotide with an enzyme that interacts with and processes along a polynucleotide, under conditions sufficient to induce enzyme activity; and (ii) detecting conformational changes in the enzyme as the enzyme processes along the polynucleotide, and thereby determining the sequence of the polynucleotide, wherein the enzyme comprises a first bound fluorescent molecule, the characteristic of which alters as the enzyme undergoes a conformational change (col. 5, lines 29 to col. 8, lines 13, 53-64 and col. 9, lines 11-28). Chan et al further teach wherein the enzyme is a helicase or a DNA polymerase (col. 7, lines 31-38). Chan et al teaches that these enzymes are useful when the

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[1] Note* The claims 28 and 30 as written lacks proper antecedent basis. Therefore, for the purpose of application of prior art, the limitation "the

target is DNA (col. 7, line 31-33). Likewise, Chan et al teach that DNA polymerases have been demonstrated to function as efficient molecular motors[2]. Chan et al state that preferably the internal diameters of the regions of the polymerase which clamp onto the DNA is similar to that of double stranded DNA, thus, large amounts of DNA can be threaded through the clamp in a linear fashion (col. 7, lines 42-46). Chan et al additionally teach that helicases are another preferred type of molar motors[1]. The reference teaches that helicases are proteins that move along nucleic acid backbones and unwind the nucleic acid so that the processes of DNA replication, repair, recombination, transcription, mRNA splicing, translation and ribosomal assembly can place (col. 8, lines 5-12). Therefore, in view of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the method of determining the sequence of a polynucleotide as taught by Korlach et al to encompass a helicase enzyme instead of a polymerase enzyme. One of ordinary skill in the art would have been motivated to do with a reasonable expectation of success based on the teachings of Chan et al that a helicase enzyme is another preferred enzyme which physically interacts with a polymer and moves the polymer past a signal station (col. 8, lines 5, see also footnote 1). Additionally one of ordinary skill in the art would have been motivated based on the teaching of Chan et al that DNA polymerase or helicases or useful when the target (polymer) is DNA (col. 7, lines 31-32).

Regarding claim 26, Chan et al teach the method according to claim 25,, wherein a plurality of enzymes is immobilized on a solid support (array) (col. 11, lines 57-61 and figure 1).

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first fluorescent molecule" is being interpreted by the Examiner as "a first fluorescent molecule".

[2] Molecular motors are defined as a biological molecule that physically interacts with a polymer (nucleic acid) and moves the polymer past a signal station (col. 7, lines 28-30).

Regarding claim 32 and 34, Chan et al teaches the method as discussed above, wherein the method is carried out using a confocal microscope and wherein said optical system detects single fluorophore polarization (see lines 40-67 and col. 36, line 56 to col. 37, lines 1-4).

9. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Korlach et al as previously applied above in view of Chan et al (US 6,355,420 B1, filing date August 13, 1998). Regarding claim 33, Korlach et al teach a method for determining the sequence of a polynucleotide comprising the embodiments discussed in claim 22, wherein the enzyme is a polymerase enzyme (paragraphs 0042, 0074, 0105). Korlach et al further teach wherein the detection as required in step (ii) is determined by time-resolved far-field microspectroscopy, near -field microspectroscopy, measurement of fluorescence resonance energy transfer, photoconversio and measurement of fluorescence lifetimes (paragraph 0059, page 7, col. 1, lines 29-33).

Korlach et al differ from the instant invention in that the reference does not expressly state that the detecting step (ii) is carried out by fluorescence imaging.

Chan et al teach a method similar to that of Korlach et al for determining the sequence of a polynucleotide comprising the steps of (i) reacting a target polynucleotide with an enzyme that interacts with and processes along a polynucleotide, under conditions sufficient to induce enzyme activity; and (ii) detecting conformational changes in the enzyme as the enzyme processes along the polynucleotide, and thereby determining the sequence of the polynucleotide, wherein the enzyme comprises a first bound fluorescent molecule, the characteristic of which alters as the enzyme undergoes a conformational change (col. 35, line 16 to col. 36, line 21).

Chan et al teach further teach wherein the detecting step (ii) is carried out by fluorescence imaging 36, lines 1-13). Chan et al teach that imaging systems, such as, e.g., fluorescent imaging systems are important because they have, among other parameters, low noise, high quantum efficiency, proper pixel-to-image correlation and efficient processing times (col. 36, lines 1-13). Therefore, in view of the foregoing one of ordinary skill in the art would have been motivated to have modified the method of determining a sequence of a polynucleotide as taught by Korlach et al to encompass detecting the step (ii) by fluorescent imaging based on the advantages taught by Chan et al that imaging systems, such as, e.g., fluorescent imaging systems, are important because they have, among other parameters, low noise, high quantum efficiency, proper pixel-to-image correlation and efficient processing times.

10. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Korlach et al as previously applied above in view of Ha et al (Proc. Natl. Acad. Sci., USA, vol. 96, pages 893-898, February 1996). Regarding claim 35, Korlach et al teach a method for determining the sequence of a polynucleotide comprising the embodiments discussed in claim 22, wherein the enzyme is a polymerase enzyme (paragraphs 0042, 0074, 0105). Korlach et al further teach wherein the detection as required in step (ii) is determined by time-resolved far-field microspectroscopy, near -field microspectroscopy, measurement of fluorescence resonance energy transfer, photoconversio and measurement of fluorescence lifetimes (paragraph 0059, page 7, col. 1, lines 29-33).

Korlach et al differ from the instant invention in that the reference does not expressly state that the detecting step (ii) is carried out by fluorescence polarization anisotrophy (FPA).

However, FPA is well known and commonly used in the art to assess the effects of a ligand binding on a target nucleic acid's stability and/or conformation.

For example in a general teaching, Ha et al teach the use of fluorescence polarization anisotropy to observe conformational fluctuations and catalytic reactions of an enzyme (e.g., *staphylococcal* nuclease (SNase)) at single molecule resolution (page 893, col. 1, last five lines of second paragraph). Ha et al teach that to probe the conformational dynamics of SNase and its interactions with substrate at single molecule resolution, three separate experiments were performed, one of which comprised doubly labeling the SNase enzyme with a donor and acceptor fluorophore and measuring fluorescence polarization anisotropy (abstract and Figure 3 & legend). Ha et al disclose that that the method revealed distinct patterns of fluctuations that may be attributed to protein conformational dynamics on the millisecond time scale (abstract). Likewise, the reference teaches that the method is useful in studies of protein folding and enzyme catalysis at single molecule resolution (Abstract). Therefore, in view of the teachings of Ha et al, one of ordinary skill in the art would have been motivated at the time of the claimed invention to have been motivated to have modified the method of determining a sequence as taught by Korlach et al to encompass detecting conformation changes of the enzyme by fluorescence polarization anisotropy. One of ordinary skill in the art would have been motivated to do so for the benefits taught by Ha et al. that fluorescence polarization anisotropy is useful in studies of protein folding and enzyme catalysis at single molecule resolution.

Conclusion

11. No claims are allowed. However, the claims 41, 43, 45 and 46 were not rejected under prior art because no prior art was found teaching a solid support comprising at least one immobilized polymerase or helicase enzyme wherein the enzyme is labeled with at least one fluorescent resonance energy transfer donor label *and* at least one fluorescent resonance energy transfer acceptor label. The closest prior art, Chan et al (US 6,210896) teach a solid support and apparatus, wherein said solid support comprises at least one immobilized polymerase or helicase enzyme, wherein said polymerase or helicase enzyme comprises at least one fluorescent resonance energy transfer donor label *or* at least one fluorescent resonance energy transfer acceptor label.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER
9/2/2004